REMARKS/ARGUMENTS

I. SUPPORT FOR THE CLAIM AMENDMENTS

Claims 55, 72-74, 78, 80, 81, 83, and 89 have been amended and claim 77 has been canceled solely to expedite prosecution.

Support for the claim amendments can be found throughout the specification and figures, as well as in the originally presented claims. Accordingly, no new matter has been introduced by way of these amendments claims. Entry of these amendments is respectfully requested.

II. THE PRESENTLY CLAIMED INVENTION

The presently claimed invention provides methods for delivering a double-stranded oligomer into the cytosol of a cell. The methods comprise contacting the cell with said at least one double-stranded oligomer and a fluorophore. After the double-stranded oligomer and fluorophore are taken up by the cell, the cell is irradiated with radiant energy at a wavelength that activates the fluorophore, which will, in turn, cause the release of the double-stranded oligomer into the cytosol of the cell. In one embodiment of the presently claimed invention, the fluourophore is delivered to the cell *via* a fluorescently labeled transport peptide.

III. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH ARE MOOT

In the Office Action dated November 15, 2005, the Examiner rejected 55-94 under 35 U.S.C. §112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." *Prosecution History of U.S. Serial No. 10/071,512, Office Action of November 15, 2005,* page 2. Without agreeing with the Examiner's assertions, Applicant has amended claims 55, 72-74, 78, 80, 81, 83, and 89 solely to expedite prosecution. The present amendments do not alter the scope of the claims.

Applicant notes that claims 76-82 were rejected because of the phrase "substantially comprised of amino acids" is allegedly unclear. Claim 76, however, does not contain such a limitation. Furthermore, claims 79-82 depend or ultimately depend upon claim 76. Claim 77, which did contain the allegedly unclear limitation, has been canceled to expedite prosecution and claim 78 has been amended to correct dependency. In light of the claim amendments and cancellation, reconsideration and withdrawal of this rejection are earnestly solicited.

IV. THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, IS TRAVERSED

In the Office Action dated November 15, 2005, the Examiner rejected 72-94 under 35 U.S.C. §112, first paragraph, as allegedly "failing to comply with the written description requirement." *Office Action of November 15, 2005,* page 3. Specifically, the Examiner states that the claims "contain new matter because the specification and claims as filed did not contemplate a fluorescently labeled transport peptide." *Office Action of November 15, 2005,* page 4. The Examiner then concludes that, based on this lack of "contemplation" "one of skill in the art could not conclude that Applicant was in possession of the claimed method at the time the application was filed." *Office Action of November 15, 2005,* page 5.

The Examiner is reminded that a specification's "contemplation" of the claimed invention is not the standard for determining if a specification complies with the written description requirement. Rather, the standard for determining if a specification complies with the written description requirement is that "the description must clearly allow persons or ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991) (quoting *In re Gosteli,* 872 F.2d 1008, 1012 (Fed. Cir. 1989)).

To support this notion of that the specification "contemplate" the claimed invention, the Examiner appears to be searching for, and requiring, the presence of *ipsis verbis* support in the specification for claims 72-94. Such a description, however, is not required in the specification to support the claims. Rather, "the disclosure as originally filed does not have to provide *in haec*

verba support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 1999). Accordingly, Applicant asserts that the specification as filed would allow one of ordinary skill in the art to recognize or visualize that presently claimed invention; albeit not in *ipsis verbis* terms. As highlighted in the Response to Office Action, filed August 29, 2005, the specification provides ample support for a fluorescently labeled transport peptide, such as, but not limited to paragraphs 0011, 0034, 0055, 0065, 0075, 0088, 0089, 0106, 0114 and 0122. In particular, paragraph 0122 discusses linking fluorphores to peptides. The peptides in this paragraph are not limited to "ligand peptides" or 'transport peptides." In fact there is no explicit limitation in this paragraph as to which peptides may be labeled. Thus, one of skill in the art would understand that a peptide – any peptide – may be labeled in conjunction with the present invention.

The Examiner, on the other hand, appears to be relying upon a paragraph heading (paragraph 0117) to impart a limitation on the discussion of labeling peptides of paragraph 0122. Specifically, the Examiner states that the "specification also discusses the process of labeling peptides in the context of 'Linking of Fluorophores to Ligands." *Office Action of November 15, 2005,* page 5. Applicant asserts, however, that using a paragraph heading to limit a discussion of methods of labeling peptides is unduly restrictive and improper in reviewing a specification for adequate support. *See Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1346 (Fed. Cir. 2000) (the specification as a whole must covey to one of ordinary skill in the art, either explicitly or inherently, the claimed subject matter).

The Examiner concedes that the specification adequately supports a fluorescently labeled ligand. *See Office Action of November 15, 2005*, page 4. The transport peptides of the present claims, however, certainly qualify as "ligands" as defined in the present invention. Indeed, paragraph 0039, of the present invention states that the term ligand "includes molecules that enter cells by receptor mediated endocytosis,…." *U.S. Pregrant Publication 2003/0041655,* paragraph 0039. And one skill in the art would recognize that transport peptides can enter cells by, among other ways, receptor-mediated endocytosis. Thus, adequate disclosure exists in the

specification to support a fluorescently labeled transport peptide. Accordingly, the specification taken as whole would allow one of skill in the art to visualize the presently claimed invention.

The Examiner also notes that claim 78 contains "a broad term that embraces peptides with multiple arginine residues, a few of which are disclosed in the specification, as well as arginine homopolymer peptides that are not supported by the specification." *Office Action of November 15, 2005,* page 6. Once again, the Examiner appears to be improperly seeking *ipsis verbis* support for every possible embodiment of the present claims. Such support is not required. Indeed, "[a] specification may, within the meaning of 35 U.S.C. §112 ¶1, contain written description of a broadly claimed invention without describing all species that claim encompasses." *Utter v. Hiraga,* 845 F.2d 993,998 (Fed. Cir. 1988).

The written description requirement only requires that one of skill in the art could read the disclosure and visualize what is claimed. *See Enzo Biochem, Inc. v. Gen-Probe Inc.* 296 F.3d 1316, 1329 (Fed. Cir 2002). The fact that the Examiner could himself read the disclosure and put forth additional examples of arginine homopolymer peptides that may not be explicitly disclosed (*See Office Action of November 15, 2005,* page 6) demonstrates that the specification provides adequate support for the full scope of embodiments of "poly-arginine peptides." Thus, the Examiner's own statement supports the notion that the specification provides adequate support for the full scope of the claimed invention.

Reconsideration and withdrawal of the written description rejection are earnestly solicited.

V. THE REJECTION UNDER 35 U.S.C. §102 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 72, 74, 75, 77, 78 and 83-87 under 35 U.S.C. §102(e) as allegedly "being anticipated by Berg et al (US Patent 6,680,301, issued 1/20/04)." *Office Action of November 15, 2005,* page 6. In making the rejection, the Examiner states Berg teaches "a method for releasing molecules into the cytosol of

cells by ...treating the cells with a fluorescent photosensitizer that localizes to endosomes, ..." *Office Action of November 15, 2005,* page 6.

Applicant disagrees with the Examiner's assertion that Berg anticipates the claims. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Vertegaal Bros. v Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Berg does not teach a fluorescently labeled transport peptide as the present claims require. The Examiner relies upon Berg, col. 2, ll. 51-54 and concludes that "Berg is considered to teach a fluorescently labeled transport peptide." *Office Action of November 15, 2005,* page 7. A careful reading of the passage upon which the Examiner relies, however, shows that it is the photosensitizers of Berg that may be conjugated to "suitable carriers," rather than fluorescent labels as the present claims require. The differences between the photosensitizers of Berg and the fluorescent labels of the present invention are not trivial. The photosensitizers of Berg are large, complex molecules, most of which bind metal and all of which can be toxic to cells. Furthermore, Berg's photosensitizers are well known in the art as molecules that are excited by light and are transformed into an *excited triplet state.* The fluorescent labels of the present invention, on the other hand, generally are excited by light and decay to only to a singlet state rather than an excited triplet state. Thus, the photosensitizers of Berg are not the fluorescent labels of the present invention. The art-recognized differences between the photosensitizers of Berg and the fluorescent labels of the present invention are discussed further below.

The data in Berg highlight the differences between the fluorescent compounds of the present invention and the photosensitizers that Berg uses. Figure 14 of Berg shows the "relocalization" of fluorescently-labeled ribozymes ("FITC-ribozymes") after irradiating cells containing the photosensitizer $AlPcS_{2a}$. Berg uses the FITC compound to simply trace the movements of the ribozymes within the cell, but does not use FITC to release the ribozyme into the cytosol. Most notably, Berg does not report any "relocalization" of FITC-labeled ribozymes into the cytosol in the absence of photosensitizers.

In fact, reviewing the methods of Example 13 of Berg shows that the FITC-labeled ribozymes in cells containing the photosensitizer did not "relocalize" into the cytosol, even after being exposed to visible light. Both irradiated (exposure to red light) and non-irradiated cells were "observed" using fluorescence microscopy and phase-contrast microscopy. The mere act of "observing" the cells to collect data would thus expose the cells to light. But Berg reports that non-irradiated cells, *i.e.*, cells that were not irradiated with red light (*see* col. 12, ll. 35-37) but were exposed to visible light to collect data, did not exhibit relocalization of the FITC-ribozyme into the cytosol. Thus, although the cells containing FITC were exposed to light, the FITC molecules in Berg were not activated and subsequently released into the cytosol. Thus, Berg does not teach the use of the fluorescent compounds of the present invention to facilitate delivery of an oligomer into the cytosol of a cell.

Moreover, even if all the elements of the present invention are present in Berg, the cited reference would not enable one of skill in the art to make and use the presently claimed invention. Indeed, the previous discussion regarding the differences between the photosensitizers of Berg and the fluorescent compounds of the present invention also demonstrates that Berg lacks any teachings on methods of delivering an oligomer into the cytosol of a cell using a fluorescently labeled transport peptide. Beyond poly-arginine, Berg is silent towards using transport peptides to facilitate delivery of an oligomer across a cell membrane. And Berg is silent towards conjugating a fluorescent molecule to any type of transport peptide. In addition, Berg is silent towards correlating any fluorescent labels with an excitation wavelength that will facilitate the release of an oligomer into the cytosol of a cell without causing toxicity. In fact, because Berg is silent on using fluorescent labels for anything other than tracking compounds, one of skill in the art would read the examples of Berg and conclude that a photosensitizing agent, as taught by Berg, would be ***required*** to release oligomers into the cytosol of the cell and that fluorescent labels alone would not suffice. Accordingly, Berg does not anticipate the claims of the present application. Reconsideration and withdrawal of this anticipation rejection are earnestly solicited.

VI. THE REJECTIONS UNDER 35 U.S.C. §103 ARE TRAVERSED

A. THE REJECTION OF CLAIMS 55, 57, 58, 60-64, 72, 74, 75 AND 83-87 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 55, 57, 58, 60-64, 72, 74, 75 and 83-87 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Fire et al (US Patent 6,506,559, issued 1/14/03)...." *Office Action of November 15, 2005,* page 8.

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach *every* limitation of the currently claimed invention, *In re Royka,* 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991).

The deficiencies of Berg have been discussed herein, and Fire does not cure these deficiencies. Like Berg, Fire does not disclose methods for delivering an oligomer into the cytosol of the cell comprising the use of fluorescently labeled transport peptide. The Examiner cites Fire because allegedly teaches "methods of inhibiting protein expression by administration of double-stranded RNAs of at least 25 nucleotides." *Office Action of November 15, 2005,* page 9. But the combination of Berg and Fire still does not teach each and every limitation of the presently claimed invention. Furthermore, there is no motivation to combine Berg and Fire. In fact, the Examiner does not address the essential element of motivation in rejecting the claims as allegedly being obvious. Reconsideration and withdrawal of the obviousness rejection of claims 55, 57, 58, 60-64, 72, 74, 75 and 83-87 under 35 U.S.C. §103 are earnestly solicited.

B. THE REJECTION OF CLAIMS 56 AND 73 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 56 and 73 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Summerton (Biochim. et Biophys. Acta 1489:141-158, 1999)." *Office Action of November 15, 2005,* page 10.

The deficiencies of Berg and Fire were previously discussed and Summerton does not cure these deficiencies. The combination of Berg, Fire and Summerton does not teach each and every limitation of the claimed invention. In particular, the combination does not disclose methods for delivering an oligomer into the cytosol of the cell comprising the use of fluorescently labeled transport peptide. Furthermore, the Examiner states that one of skill in the art "would have been motivated to [use morpholino oligonucleosides] in order to increase the resistance of the oligonucleotides extracellular nucleases that might prevent delivery of intact olgionucleotides to cells." *Office Action of November 15, 2005,* page 11. This statement, however, is a conclusion without any evidentiary basis. Thus, the Examiner does not provide any evidence that one of skill in the art would be motivated to combine the teachings of Berg, Fire and Summerton to arrive at the claimed invention. Furthermore, if one were to combine the references, there would be no reasonable expectation of success. Namely, there could be no expectation of success, because the combination of references would teach that the photosensitizers of Berg are required for delivery of an oligomer into the cytosol of a cell, and that such delivery is not possible with fluorescent labels alone.

Thus, the combination of Berg, Fire and Summerton does not render claims 56 and 73 obvious. Reconsideration and withdrawal of this rejection are earnestly solicited.

C. THE REJECTION OF CLAIMS 59 AND 76-78 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 59 and 76-78 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301,

issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Flower et al (US Patent 6,443,976, issued 9/2/02)." *Office Action of November 15, 2005,* page 11.

The deficiencies of Berg and Fire were previously discussed and Flower does not cure these deficiencies. The combination of Berg, Fire and Flower does not teach each and every limitation of the claimed invention. In fact, Flower reinforces Applicant's previous discussion regarding the differences between fluorescent labels and photosensitizers. Flower categorizes compounds such as fluorescent labels as "radiation-absorbing dyes" and photosensitizers as "photodynamic dyes." *See Flower,* abstract. Furthermore, the passage upon which the Examiner relies in Flower is a discussion of the theoretical mechanism of action of these *photodynamic dyes* rather than fluorescent labels. Flower carefully distinguishes these "radiation-absorbing dyes" and "photodynamic dyes" throughout the specification. Even the claims of Flower delineate differences between photodynamic dyes (photosensitizers) and fluorescent labels. For example, claim 9 provides a list of dyes that are "useful for photodynamic therapy" that is similar to the list of photosensitizing agents in Berg. Claim 3, however, provides a list of dyes that are "useful for dye-enhanced photocoagulation" that is similar to the list of fluorescent labels of the present invention. Clearly, even an inventor familiar with both photosensitizing agents and fluorescent labels, let alone one of ordinary skill in the art, would not consider the photosensitizers of Berg to be the same as the fluorescent dyes of the present application. Consequently, Applicant disagrees with the Examiner's statement that "fluorescein is a functional equivalent of the fluors of Berg." *Office Action of November 15, 2005*, page 12. To the contrary, Flower's treatment of fluorescein demonstrates that it is not considered a functional equivalent to "the fluors of Berg." Accordingly, the combination of Berg, Fire and Flower does not contain each and every elements of the present invention.

Flower's treatment of photodynamic dyes and radiation-absorbing dyes also provides credence to Applicant's assertion that one of skill in the art would not have any reasonable expectation of success in delivering an oligomer to the cytosol of a cell, without the use of these

toxic photosensitizing agents listed in Berg and Flower. Furthermore, there is no motivation in the references to substitute the photosensitizers of Berg with the fluorescent labels of the present invention, since the two classes of compounds are not "art-recognized equivalents".

Thus, the combination of Berg, Fire and Flower does not render claims 59 and 76-78 obvious. Reconsideration and withdrawal of this rejection are earnestly solicited.

D. THE REJECTION OF CLAIMS 65 AND 88 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 65 and 88 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Parker [et] al (US Patent 5,541,438, issued 9/17/85)." *Office Action of November 15, 2005,* page 13.

The deficiencies of Berg and Fire were previously discussed and Parker does not cure these deficiencies. The combination of Berg, Fire and Parker does not teach each and every limitation of the claimed invention. The Examiner cites Parker because Parker allegedly teaches "an endoscopic light source capable of delivering excitatory wavelengths of light ...." *Office Action of November 15,* page 13. The combination of Berg, Fire and Parker, however, still does not teach or suggest the methods of the claimed invention.

Accordingly, Applicant asserts the combination of Berg, Fire and Parker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Thus, the combination of Berg, Fire and Parker does not render obvious claims 59 and 76-78. Reconsideration and withdrawal of this rejection is earnestly solicited.

E. THE REJECTION OF CLAIMS 66-70 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 66-70 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Pandey (US Patent 5,002,962)." *Office Action of November 15, 2005,* page 14.

The deficiencies of Berg and Fire were previously discussed and Pandey does not cure these deficiencies. The combination of Berg, Fire and Pandey does not teach each and every limitation of the claimed invention. The Examiner cites Pandey because it allegedly teaches that it "was routine in the art at the time of filing to conjugate photosensitizers to other molecules by covalent means." *Office Action of November 15,* page 15. Once again, Pandey reinforces Applicant's position that photosensitizing agents are not the fluorescent labels used in the present methods. Pandey, which is entitled "Photosensitizing Agents," discusses compounds similar to the list of compounds disclosed in Berg, but makes no mention of the fluorescent labels used in the methods of the present invention. Pandey does not discuss, for example, covalently attaching a fluorescein molecule to other compounds. Thus, Pandey does not teach covalent attachment of the fluorescent labels of the present invention to other molecules. Accordingly, the combination of Berg, Fire and Pandey does not teach each and every limitation of the presently claimed invention.

Furthermore, there is no motivation found in the references to combine Berg, Fire and Pandey to arrive at the claimed invention, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg, Fire and Pandey cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Thus, the combination of Berg, Fire and Pandey does not render obvious claims 66-70. Reconsideration and withdrawal of this rejection are earnestly solicited.

F. THE REJECTION OF CLAIM 71 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claim 71 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Pandey (US Patent 5,002,962) and Parker (US Patent 4,541,438, issued 9/17/85)." *Office Action of November 15, 2005,* page 15.

The deficiencies of Berg, Fire and Pandey were previously discussed and, similar to the discussion regarding Parker, Parker does not cure these deficiencies. The combination of Berg,

Fire, Pandey and Parker does not teach each and every limitation of the claimed invention. The Examiner cites Parker because Parker allegedly teaches "an endoscopic light source capable of delivering excitatory wavelengths of light ...." *Office Action of November 15,* page 13. The combination of Berg, Fire, Pandey and Parker, however, still does not teach or suggest the methods of the presently claimed invention.

Furthermore, there is no motivation found in the references to combine Berg, Fire, Pandey and Parker to arrive at the claimed invention, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg, Fire, Pandey and Parker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Thus, the combination of Berg, Fire, Pandey and Parker does not render obvious claim 71. Reconsideration and withdrawal of this rejection is earnestly solicited.

G. THE REJECTION OF CLAIMS 79, 80 AND 82 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 79, 80 and 82 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Flower et al (US Patent 6,443,976, issued 9/2/02) and Baetge et al (US Patent 6,451,601)." *Office Action of November 15, 2005,* page 17.

The deficiencies of Berg, Fire and Flower were previously discussed and Baetge does not cure these deficiencies. The combination of Berg, Fire, Flower and Baetge does not teach each and every limitation of the claimed invention. The Examiner cites Baetge because Baetge allegedly teaches that "polylysine, antennapedia, TAT and VP22 function[] similarly in that they facilitate translocation of attached molecules across membranes." *Office Action of November 15,* page 17.

The combination of Berg, Fire, Flower and Baetge, however, still does not teach or suggest the methods of the present invention. Baetge discloses fusion proteins of "translocation moieties" and other polypeptides. On the other hand, the methods of the present invention are

directed towards delivering nucleic acids across a cell membrane and do not require attachment of the transport peptide to another protein or peptide sequence. Furthermore, the presently rejected claims do not require attachment of the transport peptide with the oligomer. Because Baetge discloses transport of proteins across cell membranes, rather than oligomers, one of skill in the art would not be motivated to even review Baetge, let alone combine or modify the collective teachings of Berg, Fire and Flower with Baetge. The Examiner appears to be using the present specification as a blueprint for hindsight picking and choosing of elements from the cited references, and such an exercise is not permitted in an obviousness analysis. And as the Federal Circuit has held numerous times, this type of hindsight analysis is impermissible. Instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.")

Thus, the combination of Berg, Fire, Flower and Baetge does not render claims 79, 80 and 82 obvious. Reconsideration and withdrawal of this rejection are earnestly solicited.

H. THE REJECTION OF CLAIMS 79-82 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 79-82 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Flower et al (US Patent 6,443,976, issued 9/2/02) Baetge et al (US Patent 6,451,601) and Rosenecker et al (US Published Application 20030125242, published 7/3/2003)." *Office Action of November 15, 2005,* page 18-19.

The deficiencies of Berg, Fire, Flower and Baetge were previously discussed and Rosenecker does not cure these deficiencies. The combination of Berg, Fire, Flower, Baetge and Rosenecker does not teach each and every limitation of the claimed invention. The Examiner cites Rosenecker because Rosenecker allegedly teaches that "HIV-TAT, Antennapedia and Transportan were functionally equivalent for the purpose of transferring molecules into cells."

Office Action of November 15, 2005, page 19. The combination of Berg, Fire, Flower, Baetge and Rosenecker however, still does not teach or suggest a method of delivering an oligomer into the cytosol of a cell using the methods of the present invention.

Furthermore, in this 5-reference obviousness rejection, there is no motivation found in the references to combine Berg, Fire, Flower, Baetge and Rosenecker to arrive at the claimed invention with any reasonable expectation of success. Once again, the Examiner appears to be improperly using the present specification as guidance to comb the art in search of all elements of the claimed invention. Accordingly, Applicant asserts that the combination of Berg, Fire, Flower, Baetge and Rosenecker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

I. THE REJECTION OF CLAIMS 89-93 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claims 89-93 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Priest (US Patent 5,391,723)." *Office Action of November 15, 2005,* page 20.

The deficiencies of Berg and Fire were previously discussed and Priest does not cure these deficiencies. The Examiner cites Priest because Priest allegedly teaches "the use of pH-sensitive covalent linkers to attach double-stranded oligomers to targeting proteins for delivery of cells." *Office Action of November 15, 2005,* page 20. The combination of Berg, Fire and Priest, however, still does not teach a method of delivering an oligomer to the cytosol of a cell. Nor does the combination teach or suggest the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg, Fire and Priest to arrive at the claimed invention with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg, Fire and Priest cannot be used to establish a *prima*

facie case of obviousness against the current claims. Reconsideration and withdrawal of this rejection are earnestly solicited.

J. THE REJECTION OF CLAIM 94 UNDER 35 U.S.C. §103 IS TRAVERSED

In the Office Action of November 15, 2005, the Examiner rejected claim 94 under 35 U.S.C. §103 as allegedly "being unpatentable over ... Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03)...and further in view of Priest (US Patent 5,391,723) and Parker [et] al (US Patent 4,541,438)." *Office Action of November 15, 2005,* page 21.

The deficiencies of Berg, Fire and Priest were previously discussed and Parker does not cure these deficiencies. The combination of Berg, Fire, Priest and Parker does not teach each and every limitation of the claimed invention. The Examiner cites Parker because Parker allegedly teaches "an endoscopic light source capable of delivering excitatory wavelengths of light ...." *Office Action of November 15,* page 21. The combination of Berg, Fire, Priest and Parker, however, still does not teach or suggest the methods of the presently claimed invention.

Furthermore, there is no motivation found in the references to combine Berg, Fire, Priest and Parker to arrive at the claimed invention with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg, Fire, Priest and Parker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Thus, the combination of Berg, Fire, Priest and Parker does not render obvious claim 94. Reconsideration and withdrawal of this rejection is earnestly solicited.

CONCLUSION

Claims 55, 72-74, 78, 80, 81, 83, and 89 have been amended and claim 77 has been canceled. Entry of these amendments is respectfully requested.

The amendments to the claims render moot the rejections under 35 U.S.C. §112, second paragraph. Applicant has presented arguments traversing the rejections under 35 U.S.C. §§102(e), 103 and 112, first paragraph. Careful reconsideration and withdrawal of each of these rejections are earnestly solicited.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: April 14, 2006 By: /TBB/

Castellano Malm Ferrario & Buck PLLC
Customer Number: 57904
Telephone: (202) 478-5300
Facsimile: (202) 318-1288

Todd B. Buck
Registration No. 48,574

ND: 4845-5207-1680, Ver 1